

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number:	WO 98/26765
A61K 9/20, 31/40, 47/12		(43) International Publication Date:	25 June 1998 (25.06.98)
(21) International Application Number:	PCT/HU97/00084	(81) Designated States:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date:	15 December 1997 (15.12.97)	(30) Priority Data:	P 96 03489 18 December 1996 (18.12.96) HU
(71) Applicant (for all designated States except US):	CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT. [HU/HU]; Tó u. 1-5, H-1045 Budapest (HU).	(72) Inventors; and	
(73) Inventors/Applicants (for US only):	TÓTH, Antal [HU/HU]; Holdvilág u. 7, H-1118 Budapest (HU). CSERNÁK, László [HU/HU]; Komócsy u. 42, H-1141 Budapest (HU). KORITSÁNSZKY, Klára [HU/HU]; Iskola u. 11, H-2120 Dunakeszi (HU). SALAMON, Endréne [HU/HU]; Kiscelli u. 68, H-1032 Budapest (HU). VENCZEL, Márta [HU/HU]; Aranyvirág s. 5, H-1098 Budapest (HU). VÉGELI, Erzsébet [HU/HU]; Csuka u. 2, H-1131 Budapest (HU).	(74) Common Representative:	CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT.; Industrial Property Rights, Tó u. 1-5, H-1045 Budapest (HU).

(54) Title: STABILIZED PHARMACEUTICAL COMPOSITIONS AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

The invention relates to pharmaceutical compositions of enalapril maleate stabilized by maleic acid.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Israel	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Stabilized pharmaceutical compositions and process for the preparation thereof

The present invention relates to novel stabilized pharmaceutical compositions, process for their preparation and the use of maleic acid as a stabilizer. The active ingredient of the above
5 compositions is enalapril maleate which is a potent angiotensin-converting enzyme inhibitor, and it is useful in the treatment of hypertension.

Enalapril, its salts and the process for their preparation are described in the European Patent Application publ. No. EP-012401 A1.

10

As it is known, many compounds that inhibit ACE (Angiotensin-Converting Enzyme) have poor stability either in form of free acids or salts if they are in a pharmaceutical dosage form. These compounds easily decompose first of all by hydrolysis and intramolecular cyclization, but the amount of other decomposition products not identified in many cases may be also significant. This is
15 particularly true in case of enalapril and its maleate salt.

Main decomposition products of enalapril are shown in Fig. demonstrating that the decomposition is due to hydrolytic and cyclization processes.

20 The diketopiperazine (DPK) is the internal cyclization product and the diacid (enalaprilat ET) is the product of ester hydrolysis.

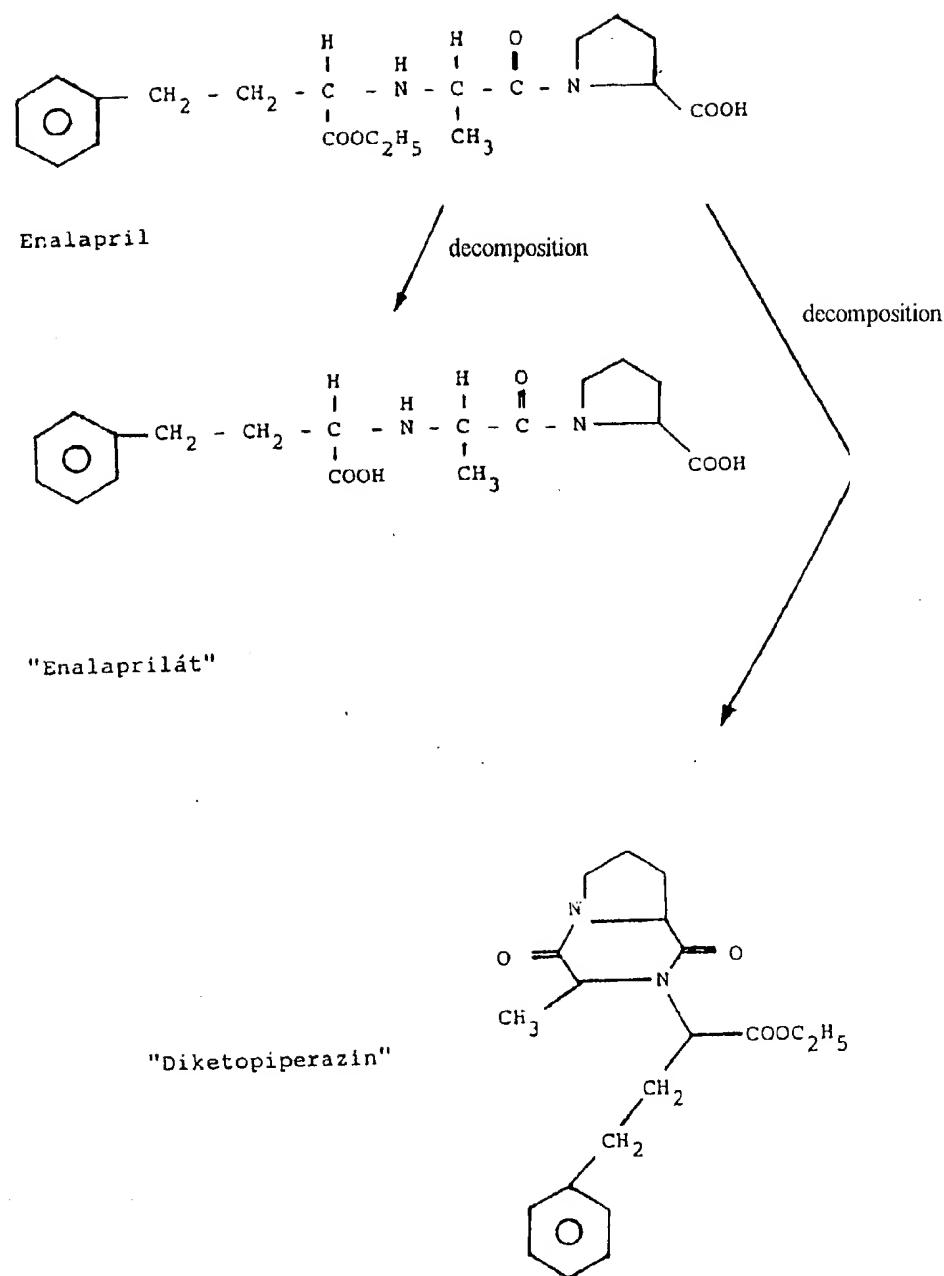
A lot of solutions have been elaborated to stabilize angiotensin-converting enzyme inhibitors, among them enalapril salts in pharmaceutical compositions.

25

According to the European Patent Application publ. no. EP-0 280 999 A2, magnesium carbonate shows a stabilizing effect in pharmaceutical products containing saccharides, e.g. lactose and quinapril.

30 According to the European Patent Application publ. no. EP-0 545 194 A1, enalapril is transformed into its sodium salt. The enalapril sodium salt in pharmaceutical preparations is said to be more stable than the enalapril maleate salt.

Fig.



United States Patent no. 5.562.921 describes that the enalapril maleate salt extensively decomposes in the presence of commonly used vehicles, filling substances, lubricants or disintegrating agents in many pharmaceutical products for example in the pharmaceutical dosage forms containing microcrystalline cellulose, calcium phosphate or magnesium stearate.

- 5 It is described in EP-A-099239 and EP-B-0264887 that ascorbic acid may be used as an antioxidant or colour stabilizing agent in case of ACE-inhibitors.

The aim of our invention is to prepare pharmaceutical formulations of high stability which contain enalapril maleate with commonly used filling substances (e.g. lactose, mannitol, sorbitol) lubricant 10 (e.g. magnesium stearate) and disintegrating agents (e.g. starch) and in which the amount of decomposition products is low even in case of long-term storage, thus ensuring a longer expiration time and in the same time a high quality.

It has been found that if enalapril maleate is transformed into pharmaceutical formulations by 15 applying commonly used filling substance (e.g. filling substance of saccharide type) and maleic acid stabilizer, an extremely stable enalapril formulation is obtained. This is true even if magnesium stearate or other compounds are used as lubricants, affecting the stability of enalapril maleate .

At realizing our invention, we have successfully applied for example mono- or disaccharides, water- 20 free lactose, lactose monohydrate or DC (direct compression) lactose as filling substances, starches or partly hydrolysed starches, or crospovidone (polyvinylpolypyrrolidone) as disintegrating agents, magnesium stearate, hydrogenated vegetable oil or talc as lubricants, and maleic acid as stabilizer, in addition to the currently used colouring and binding agents, e.g. ferric oxide and povidone (polyvinylpyrrolidone). Further auxiliary substances applicable for these purposes are enumerated in 25 the Hungarian Pharmacopoeia or in the European Pharmacopoeia.

One of the preferred variant forms of our invention is the tablet or the granules for filling capsule consisting of enalapril maleate, maleic acid, lactose, starch, partly hydrolysed starch and magnesium stearate, and optionally colouring and binding agents.

- 30 Our invention also relates to the process for the preparation of the above pharmaceutical formulations. During this process, granules to be compressed in tablets or to be filled into capsules are prepared by wet granulation using aqueous solution of maleic acid.

During one of the favourable implementations of the above process, dry enalapril maleate, lactose, starch and partly hydrolysed starch are mixed, and then their mixture is granulated using aqueous solution of maleic acid used as granulation liquid. Of course, ingredients may be mixed in other sequences. The granules obtained are dried and classified, and then compressed into tablets with magnesium stearate added.

Tablets according to our invention can be prepared by direct tabletting, i.e. mixing enalapril maleate with all other auxiliary substances and with maleic acid used as stabilizing agent, and by compressing the mixture in tablets.

Pharmaceutical products (dosage forms) prepared according to our invention may preferably contain enalapril maleate in 0.1-25 weight %, lactose in 30-95 weight %, starch and partly hydrolysed starch in 6-80 weight %, maleic acid in 0.1-10 weight %, lubricant in 0.1-5 weight % and colouring and binding agents in 0.01-5 weight %.

Preferred dosage forms are tablets and granules which contain enalapril maleate in 1.5-15 weight %, lactose in 65-90 weight %, starch and/or other disintegrating agents in 5-15 weight %, binding and colouring agents in 3-7 weight %, pregelatinized starch in 1-4 weight %, maleic acid in 1-5 weight % and lubricants in 0.1-1.5 weight %. Most preferred unit dosage forms are tablets with 75-300 mg tablet mass having above preferred compositions.

Further details of our invention are shown by the examples below, without limiting our claims to the examples.

Examples**Example 1**

- 5 100 g of enalapril maleate, 3930 g of lactose monohydrate, 380 g of corn starch, 120 g of pregelatinized starch were homogenized. 24 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 20 g of magnesium stearate (for 10-20 min).
- 10 The homogenized granules were tabletted and tablets having 115 mg total mass and containing 2.5 mg of enalapril maleate were obtained.

Example 2

- 15 150 g of enalapril maleate, 5934 g of lactose monohydrate, 570 g of corn starch, 180 g of pregelatinized starch were homogenized. 36 g of maleic acid was dissolved in 1500 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 30 g of magnesium stearate (for 10-20 min).
- 20 The homogenized granules were tabletted.

Example 3

- 200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 950 ml purified water. The homogenized powder mixture was granulated by slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

Example 4

250 g of enalapril maleate, 1890 g of lactose monohydrate, 188 g of corn starch, 68 g of pregelatinized starch were homogenized. 60 g of maleic acid was dissolved in 600 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 45 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted and tablets having 200 mg total mass and containing 20 mg of enalapril maleate were obtained.

10

Example 5

200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch, 48 g of maleic acid were homogenized. The homogeneous powder mixture was granulated with slowly (10-15 min) added purified water (950 ml). The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized mixture was tabletted.

20 **Example 6**

3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 1100 ml of purified water. While stirring, 200 g of enalapril maleate was added. The homogeneous powder mixture was added to the suspension. 25 The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.

The homogenized granules were tabletted.

Example 7

30

250 g of enalapril maleate, 4200 g of lactose monohydrate, 370 g of corn starch, 120 g of pregelatinized starch were homogenized. 45 g of maleic acid was dissolved in 1300 ml of purified water. While stirring, 120 g of polyvinylpyrrolidone was added to the pure solution. The

homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid and polyvinylpyrrolidone. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

5

Example 8

10 250 g of enalapril maleate, 60 g of maleic acid, 45 g of magnesium stearate, 120 g of polyvinylpyrrolidone, 120 g of pregelatinized starch were homogenized. 370 g of corn starch, 4200 g of lactose monohydrate were added to the homogeneous mixture and the mixture was homogenized again (for 15-20 min).

The homogeneous mixture was tabletted.

Example 9

15

200 g of enalapril maleate, 1600 g of lactose monohydrate, 1600 g of corn starch, 250 g of pregelatinized starch, 100 g of polyvinylpyrrolidone, 150 g of talc were homogenized. 50 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.

The homogenized granules were tabletted.

Example 10

25 200 g of enalapril maleate, 250 g of pregelatinized starch were homogenized, 100 g of polyvinylpyrrolidone, 150 g of talc, 50 g of maleic acid and 40 g of magnesium stearate were homogenized. To the homogeneous mixture 1600 g of lactose and 1600 g of corn starch were added. The mixture was homogenized (for 15-20 min).

The homogenized mixture was tabletted.

30

Example 11

100 g of enalapril maleate, 1700 g of lactose monohydrate, 40 g of crospovidone, 110 g of maize
5 starch and 2 g of ferrous oxide red were homogenized. 48 g of maleic acid was dissolved in 1200 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried at 40-50°C. The dried granules were homogenized with 10 g of magnesium stearate for 20 min.. The homogenized granules were
10 tabletted and tablets having 200 mg total mass and containing 10 mg of enalapril maleate were obtained.

CLAIMS

1. Stable pharmaceutical composition, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent and one or more auxiliary substances.

5

2. Composition according to claim 1, characterized in that, it contains enalapril maleate in 1.5-15 weight %, filling substances in 65-90 weight %, disintegrating agents in 6-20 weight %, maleic acid in 1-5 weight %, binding and colouring agents in 3-7 weight % and lubricants in 0.1-1.5 weight %.

10

3. Composition according to claim 1, characterized in that, it contains mono- or disaccharides as filling substance, starches and/or crospovidone as disintegrating agent, stearate salts or esters, or hydrogenated vegetable oils as lubricants.

15

4. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose as filling substance, starch and crospovidone as disintegrating agent, magnesium stearate, hydrogenated vegetable oil or talc as lubricant, povidone as binding agent and optionally ferric oxide as colouring agent.

20

5. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose monohydrate as filling substance, starch as disintegrating agent, magnesium stearate as lubricant and optionally ferric oxide as colouring agent.

6. Composition according to claim 1, characterized in that, the dosage form is a tablet.

25

7. Composition according to claim 6, characterized in that, the dosage form is a tablet having 75-300 mg of tablet mass.

30

8. Composition according to claim 1, characterized in that, the dosage form is a capsule filled with granules.

9. Process for the preparation of composition according to claim 1, characterized in that, wet granulation is used.

10. Process according to claim 9, characterized in that, wet granulation is carried out with aqueous solution of maleic acid used as stabilizing agent.
- 5 11. Process according to claim 9, characterized in that, the enalapril maleate, lactose, disintegrating and colouring agents are mixed, dried, aqueous solution of stabilizing maleic acid is added, the mixture is wet granulated, the obtained granules are dried, classified, mixed with lubricant and compressed into tablets.
- 10 12. Use of maleic acid to stabilize enalapril maleate in a pharmaceutical composition as defined in anyone of claims 1 to 8.
13. Use of maleic acid as stabilizing agent in the manufacture of a pharmaceutical composition containing enalapril maleate as defined in anyone of claims 1 to 8.
- 15 14. Composition according to claim 1, characterized in that, it is in a commercial package in the form of orally applicable dosage form together with instructions for its administering.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 97/00084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/40 A61K47/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 793 998 A (MURTHY KUCHI S ET AL) 27 December 1988 see abstract see column 1, line 21-27 see column 2, line 15-18 see column 3, line 34-38 see column 4, line 24 see column 4, line 43-56 see column 5, line 18-20 see column 5, line 32-41 see column 5, line 54-61 see claims 5,7,8 --- -/-/	1,6,8, 12-14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

1

Date of the actual completion of the international search

Date of mailing of the international search report

8 April 1998

17/04/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

La Gaetana, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 97/00084

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 468 929 A (SANDOZ LTD) 29 January 1992 see page 2, line 11 see page 2, line 50-53 see page 4, line 7-8 see example 5C see page 7, line 56 - page 8, line 6 -----	1,3,5-7, 9,10, 12-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 97/00084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4793998 A	27-12-88	AU 614710 B AU 7927487 A CA 1297023 A DE 3772001 A DK 543687 A EP 0264888 A FI 874593 A,B, HK 85394 A IE 61436 B JP 63104930 A KR 9600431 B NO 174765 B PH 25502 A SG 90194 G	05-09-91 28-04-88 10-03-92 12-09-91 21-04-88 27-04-88 21-04-88 26-08-94 02-11-94 10-05-88 06-01-96 28-03-94 24-07-91 14-10-94
EP 0468929 A	29-01-92	AT 400519 B AT 147691 A AU 639354 B AU 8128691 A CA 2047802 A CH 683150 A CS 9102309 A DE 4124409 A ES 2061218 T FI 913554 A,B, GB 2246296 A,B IE 66184 B IL 98934 A IT RM910554 A JP 2502849 B JP 4253923 A LU 87980 A PL 167712 B SK 278563 B RU 2075310 C	25-01-96 15-06-95 22-07-93 30-01-92 26-01-92 31-01-94 15-04-92 30-01-92 01-12-94 26-01-92 29-01-92 13-12-95 23-07-96 27-01-92 29-05-96 09-09-92 15-02-93 31-10-95 08-10-97 20-03-97